

ACE Inhibitors and Angiotensin-II Receptor Antagonists

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists (AIIIRAs) both target the renin-angiotensin system. ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II.¹ AIIIRAs antagonise the binding of angiotensin II to the AT1 receptor which mediates most of the antihypertensive effects usually associated with angiotensin II. Angiotensin II is important as it has numerous effects, including stimulation of the sympathetic nervous system, vasoconstriction, increasing aldosterone release and sodium retention, which can result in hypertension. Currently there are 11 ACE inhibitors, seven combination ACE inhibitors, seven AIIIRAs and six combination AIIIRAs available in the UK.¹ Although ACE inhibitors and AIIIRAs work at different steps of the renin-angiotensin system², they are broadly indicated for similar conditions and the National Institute for Health and Clinical Excellence (NICE) offers guidance on the use of these drugs in the following areas: Heart Failure³, Hypertension⁴, Myocardial Infarction Secondary Prevention⁵, Type 2 Diabetes⁶, and Chronic Kidney Disease.⁷

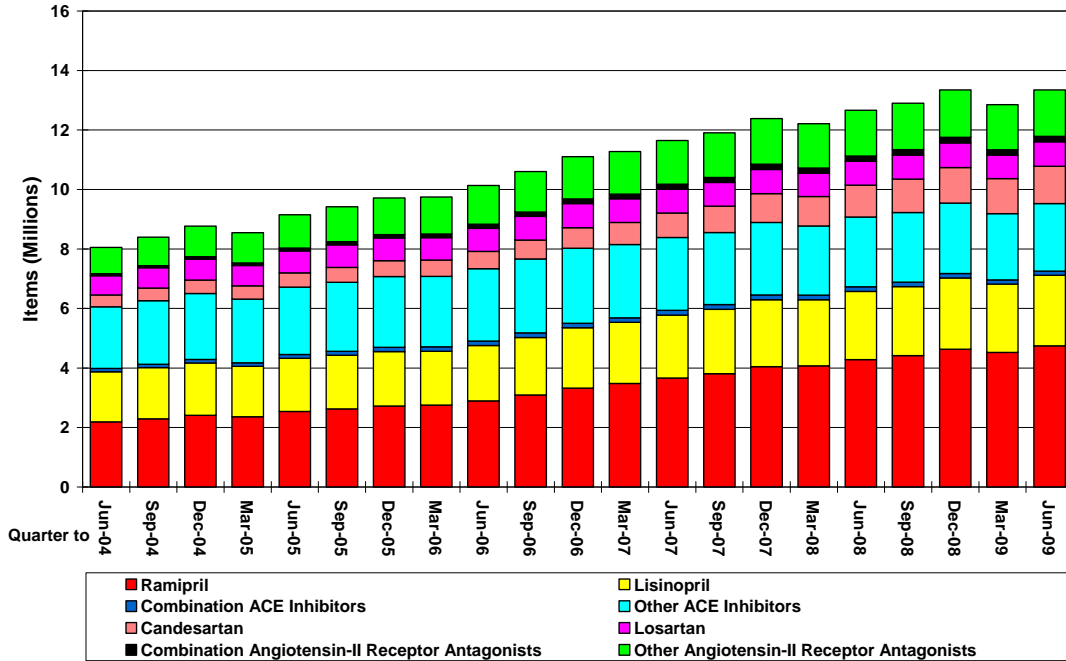
Choosing between ACE inhibitors and AIIIRAs

NICE recommends that for indications where either an ACE inhibitor or an AIIIRA could be prescribed, an ACE inhibitor is routinely the drug of choice. If either an ACE inhibitor or an AIIIRA is prescribed, NICE recommends using a drug that can be taken once a day (if possible), is generically prescribed, and minimises cost.⁴

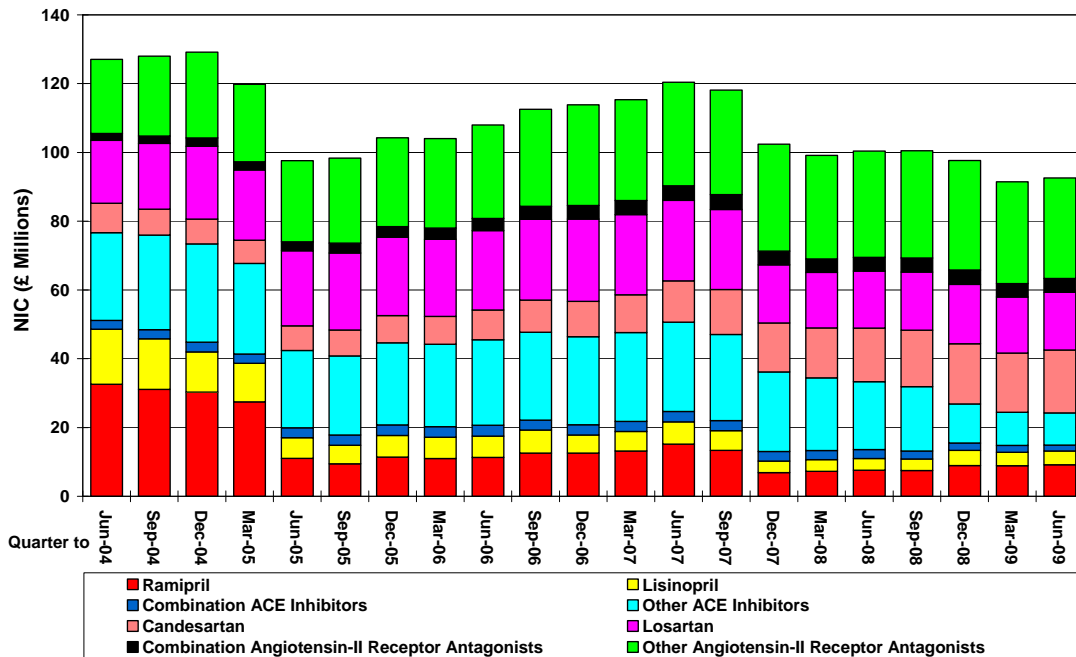
Both ACE inhibitors and AIIIRAs have a good evidence-base to support their use. However, the fact that the ACE inhibitors have been around longer has enabled a more robust evidence base to become established across all indications. There is a wide range of generic ACE inhibitor products available, unlike for AIIIRAs where there are currently none, and this makes ACE inhibitors the more cost-effective option. There is poor evidence to support the use of one ACE inhibitor over another and thus, NICE have tended to focus on recommending their place as a group in cardiovascular disease management. The same applies to AIIIRAs.

From Charts 1 and 2, ramipril is the most commonly prescribed ACE inhibitor at 4.7 million items and a cost of £9.2 million for the quarter to June 2009. Ramipril represents 50% of prescribing of ACE inhibitors and 38% of the cost. 96% of the number of items for ramipril represent prescribing of the capsule form. Lisinopril is the second most commonly prescribed ACE inhibitor and accounts for 25% of ACE inhibitor items (2.4 million) and 16% of the cost (£4 million). Of the group of 'other ACE inhibitors', perindopril (both arginine and erbumine salts) is the third most commonly prescribed ACE inhibitor. Perindopril represents only 15% of ACE inhibitor items (1.4 million) but it accounts for £6.2 million (less than a third the number of items and yet two thirds of the cost of ramipril). The Clinical Knowledge Summaries (CKS) service recommends that ACE selection should generally be limited to the use of lisinopril, ramipril or Enalapril.⁸

Trends in Prescribing of ACE Inhibitors and Angiotensin-II Receptor Antagonists in General Practice in England (Chart 1)

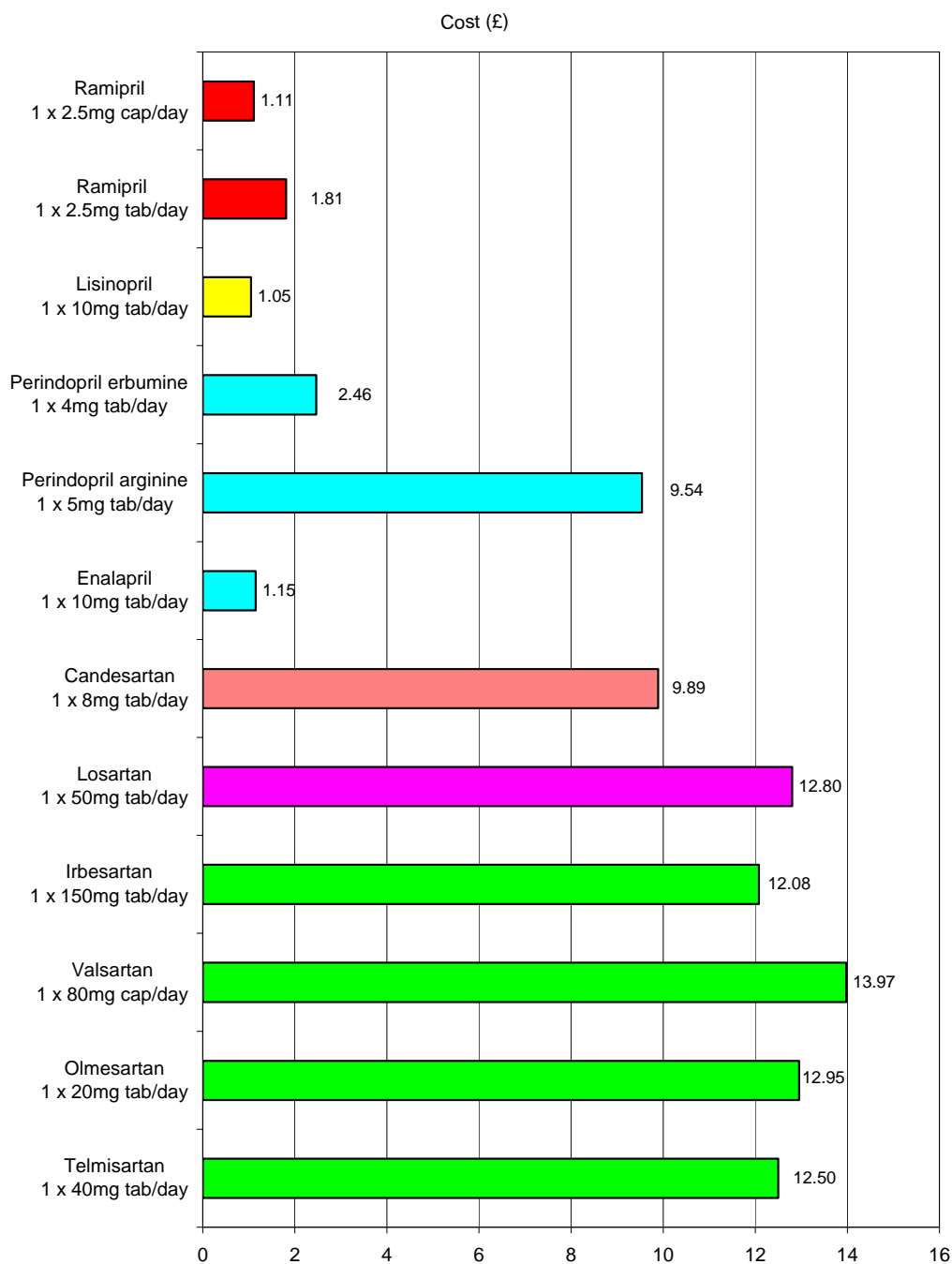


Trends in Spending on ACE Inhibitors and Angiotensin-II Receptor Antagonists in General Practice in England (Chart 2)



As can be seen from the Price Chart, lisinopril, ramipril and enalapril represent three of the most cost-effective ACE inhibitors and between them, they cover the full set of licensed indications that ACE inhibitors as a group cover. Patients' co-morbidities will also affect drug selection.

Cost for 28 Days Treatment



Prices based on Drug Tariff November 2009 and the NHS Dictionary of Medicines and Devices. Doses based on WHO DDDs where possible, otherwise BNF stated dose. The WHO DDD is a unit of measurement based on the assumed average maintenance dose in adults. It may not necessarily reflect the actual dose used.

NICE has recommended that AIIRAs are an alternative choice to ACE inhibitors when an ACE inhibitor is clinically indicated but not tolerated (due to a persistent troublesome dry cough). Good clinical practice would dictate that ideally an AIIRA should be used for a condition it is licensed for. Currently, candesartan is the most cost-effective AIIRA but the patent on losartan is due to expire March 2010 and this will enable generic products to become available. From Charts 1 and 2, in the last quarter, 1.3 million candesartan

items were prescribed at a cost of £18.3 million. This represents a similar number of items to perindopril at nearly three times the cost.

Tolerability of ACE inhibitors and AIIRAs

Unlike ACE inhibitors, AIIRAs do not inhibit the breakdown of bradykinin, and are therefore less likely to cause the persistent and troublesome dry cough that people taking ACE inhibitors may experience.¹

In a Micromedex review, the incidence of cough in patients taking ACE inhibitors has been reported to be up to approximately 12%. Among patients experiencing cough, between 20% and 60% will rate it intolerable and request withdrawal of therapy.⁹

A recent systematic review investigated the use of ACE inhibitors and AIIRAs in people with essential hypertension, and one of the comparisons looked at rates of cough.¹⁰ Rate of cough with ACE inhibitors was 9.9% compared with 3.2% for AIIRAs (absolute risk difference = 6.7%). This data was from RCTs whereas rates of cough with ACE inhibitors have been found to be notably less in observational studies. Cough is common in people with heart failure and other co-morbidities but if the cough is persistent and troublesome and if other causes have been ruled out and a renin-angiotensin type drug is indicated then NICE recommends switching to an AIIRA.

Prescribing practices to consider exploring

When considering Table 1, the distribution of AIIRAs compared with ACE inhibitors appears to represent a higher proportion of AIIRA prescribing than would be expected based on the small percentage of people who are not likely to tolerate an ACE inhibitor. At a PCT level, this variation ranges from AIIRA prescribing representing just over 20% to nearly 40% volume in terms of items. AIIRAs are significantly more costly than ACE inhibitors and NICE recommends that AIIRAs are an alternative choice to ACE inhibitors only when an ACE inhibitor is clinically indicated but not tolerated. Therefore, supporting clinicians to follow NICE guidelines and initiate patients on one of the lower cost drugs can help drive prescribing costs down.

Table 1: % Prescribing of ACE Inhibitors (excl. combination products) vs AIIRAs (excl. combination products) for the Quarter to June 2009)		
SHA	% ACE Inhibitors (excl combinations)	% AIIRAs (excl combinations)
SOUTH EAST COAST	68.34%	31.66%
LONDON	69.64%	30.36%
NORTH WEST	70.82%	29.18%
EAST OF ENGLAND	72.30%	27.70%
SOUTH CENTRAL	72.43%	27.57%
WEST MIDLANDS	72.68%	27.32%
YORKSHIRE AND THE HUMBER	72.78%	27.22%
SOUTH WEST	73.28%	26.72%
EAST MIDLANDS	73.39%	26.61%
NORTH EAST	77.15%	22.85%

Combined treatment with both an ACE inhibitor and an AIIRA currently has a limited role. For a relatively small proportion of heart failure patients who are symptomatic despite use of diuretic, beta-blocker and ACE inhibitor, options include to either add in spironolactone, or to add in an AIIRA.¹¹ Both options increase the risk of worsening renal function and hyperkalaemia, thus increased monitoring is essential. Therefore, evidence suggests that only a small proportion of patients with heart failure are eligible for consideration of combined ACE inhibitor and AIIRA use. In all other scenarios, combined treatment with an ACE inhibitor and AIIRA is not routinely recommended and recent publications have found little evidence to support this role.^{12,13}

Use of fixed-dose combination products (e.g. ACE inhibitors or AIIRAs combined with a diuretic or calcium channel blocker) is another feature which generates relatively high prescribing costs. Despite the widely held view that fixed-dose combinations improve concordance, there are few good quality studies which show this and even fewer which demonstrate improved outcomes.¹⁴ Therefore, in most situations, regimens containing single component drugs should remain the treatment of choice where possible.

Prescribing Data

(Reporting quarter = April-June 2009, Index quarter = April-June 2004)

Prescription items for ACE inhibitors and AIIRAs have increased by 66% in the last 5 years to 13.4 million items. Although the overall cost has decreased by 27% to £93million, this cost reduction can be attributed to the fact that ACE inhibitors represent 71% of items but only 26% of the cost of the drugs for these two groups combined.

Prescribing of AIIRAs has increased by 91% to 3.8 million items, with cost rising by 35% to £68.3 million. In contrast prescribing of ACE inhibitors has increased by 57% to 9.5 million items, whilst cost has decreased by 68% to £24.3 million.

Prescribing of fixed dose combination ACE inhibitor products (i.e. an ACE inhibitor combined with a diuretic or calcium channel blocker) has increased by 28% to 140,000 items, but accounts for just 1% of ACE inhibitor items prescribed. The cost of these products however represents 7% of the total cost of ACE inhibitors, although the cost that fixed dose combination ACE inhibitor products represents has decreased by 31% to £1.8million.

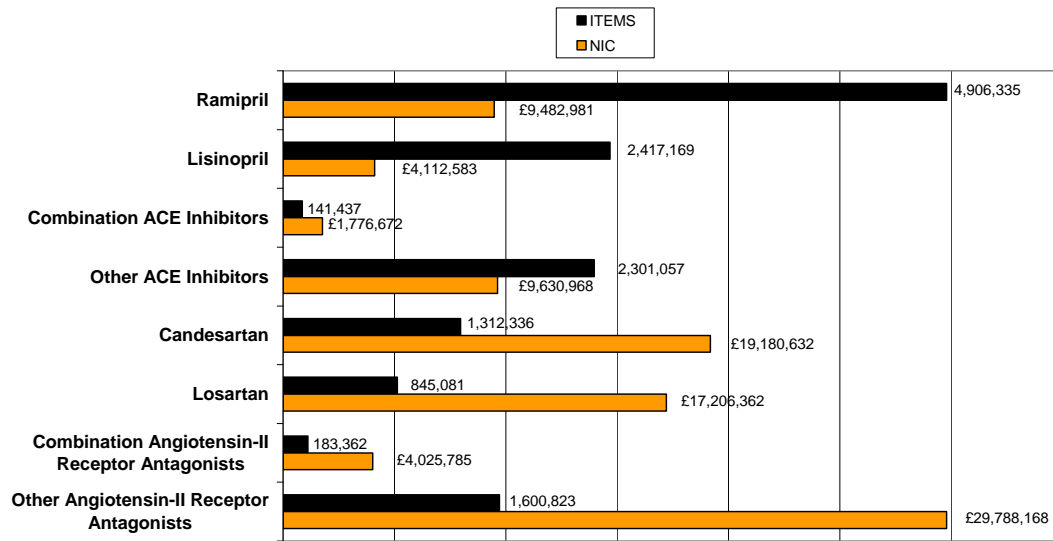
Prescribing of fixed dose combination AIIRA products (i.e. an AIIRA combined with a diuretic or calcium channel blocker) now stands at 181,000 items (a 167% increase) and costs have doubled to £4million. Combination AIIRA products account for 5% of all prescribing of AIIRAs and 6% of the cost.

1. BNF 58 (2009) BMJ Group and RPS Publishing.
2. RDTTC (2007) ACE inhibitors and angiotensin II receptor blockers in combination. Drug Update 54.
3. NICE (2003) Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. Clinical guideline 5.
4. NICE (2006) Hypertension. Management of hypertension in adults in primary care: pharmacological update. Clinical guideline 34.
5. NICE (2007) MI: secondary prevention in primary and secondary care for patients following a myocardial infarction. Clinical guideline 48.
6. NICE (2008) Type 2 diabetes: the management of type 2 diabetes. Clinical guideline 66.
7. NICE (2008) Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. Clinical guideline 73.
8. CKS (2009) Cardiovascular clinical topics. SCHIN.
9. Micromedex (2009) MICROMEDEX [CD-ROM]. (Vol 135, 3rd Quarter 2009). Thomson Healthcare.
10. Matcher DB, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med* 2008;148:16-29.
11. National Prescribing Centre. Chronic heart failure: overview of diagnosis and drug treatment in primary care. *MeReC Bulletin* 2008;18 No. 3
12. The ONTARGET investigators. Telmisartan, ramipril or both in patients at high risk for vascular events. *New Engl J Med* 2008;358:1547-59.
13. Shibata MC, et al. The effects of angiotensin-receptor blockers on mortality and morbidity in heart failure: a systematic review. *Int J Clin Pract* 2008;62:1397-402.
14. RDTTC (2008) Fixed-dose combinations (Part 2). Drug Update 62.

SUMMARY

- There is no evidence that AIIRAs are more effective than ACE inhibitors for any indication.
- AIIRAs are an alternative choice to ACE inhibitors when an ACE inhibitor is clinically indicated but not tolerated due to a persistent and troublesome dry cough.
- In a Micromedex review, the incidence of cough in patients taking ACE inhibitors has been reported to be up to approximately 12%. Among patients experiencing cough, between 20% and 60% will rate it intolerable and request withdrawal of therapy.
- Combined treatment with both an ACE inhibitor and an AIIRA currently has a limited role, and the risks of worsening renal function and hyperkalaemia are increased.
- There are few good quality studies which show that fixed dose combination products improve concordance and even fewer which demonstrate improved outcomes with their use.

**Prescribing and Spending on ACE Inhibitors and Angiotensin-II Receptor Antagonists
in England for Quarter to September 2009**



	Quarter to September 09	
	National	
	ITEMS/1000 PUs	NIC/1000 PUs
ACE Inhibitors (excl combinations)	133.64	£331.22
Combination ACE Inhibitors	1.95	£24.57
Angiotensin-II Receptor Antagonists (excl combinations)	51.97	£915.17
Combination Angiotensin-II Receptor Antagonists	2.53	£55.67